

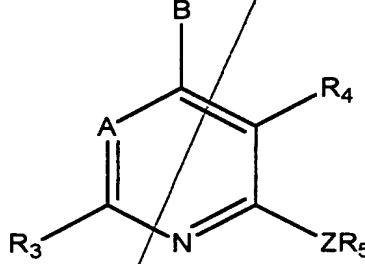
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This application is a continuation in part of Serial Number 08/741,066 filed on October 30, 1996 (now issued as Patent No 6,403,599) which claims benefit of 60/006,333 filed November 8, 1995, and also is a continuation in part of application Serial No 09/254,387 filed March 4, 1999 (now issued as Patent No 6,316,631) which is the United States part of International Patent Application PCT/IB95/00437 which was filed on June 6, 1995

IN THE CLAIMS

Please amend claims 1,2, 3 4, 14 and 15 to read as follows:

A.2
1(Amended) A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is $-\text{CR}_7$;

B is $-\text{NR}_1\text{R}_2$, $-\text{CR}_1\text{R}_2\text{R}_{11}$, $-\text{C}(\text{=CR}_2\text{R}_{12})\text{R}_4$, $-\text{NHCHR}_1\text{R}_2$, $-\text{OCHR}_1\text{R}_2$, $-\text{SCHR}_1\text{R}_2$, $-\text{CHR}_2\text{OR}_1$, $-\text{CHR}_1\text{OR}_2$, $-\text{CHR}_2\text{SR}_1$, $-\text{C}(\text{S})\text{R}_2$, $-\text{C}(\text{O})\text{R}_2$, $-\text{CHR}_2\text{NR}_1\text{R}_2$, $-\text{CHR}_1\text{NHR}_2$, $-\text{CHR}_1\text{N}(\text{CH}_3)\text{R}_2$, or $-\text{NR}_{12}\text{NR}_1\text{R}_2$;

Z is NH, O, S, $-\text{N}(\text{C}_1\text{-C}_2\text{ alkyl})$, $-\text{NC(O)CF}_3$, or $-\text{C}(\text{R}_{13}\text{R}_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl, or $-\text{C}(\text{R}_{13}\text{R}_{14})$ is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R_5 , which ring optionally comprises two or three further hetero members selected independently from oxygen, nitrogen, NR_{12} , and S(O)_m , and optionally comprises from one to three double bonds, and is optionally substituted with halo, $\text{C}_1\text{-C}_4$ alkyl, $-\text{O}(\text{C}_1\text{-C}_4\text{ alkyl})$, NH_2 , NHCH_3 , $\text{N}(\text{CH}_3)_2$, CF_3 , or OCF_3 , with the proviso that said ring does not contain any $-\text{S-S-}$, $-\text{S-O-}$, $-\text{N-S-}$, or $-\text{O-O-}$ bonds, and does not comprise more than

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B
two oxygen or $S(O)_m$ heterologous members;

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R_1 is $C(O)H$, $C(O)(C_1-C_6$ hydrocarbyl), $C(O)(C_1-C_6$ hydrocarbylene)(C_3-C_8 cyclohydrocarbyl), $C(O)(C_3-C_8$ cyclohydrocarbylene)(C_3-C_8 cyclohydrocarbyl), $C(O)(C_1-C_6$ hydrocarbylene)(C_4-C_8 heterocyclohydrocarbyl), $-C(O)(C_3-C_8$ cyclohydrocarbylene)(C_4-C_8 heterocyclohydrocarbyl), C_1-C_6 hydrocarbyl, C_3-C_8 cyclohydrocarbyl, C_4-C_8 heterocyclohydrocarbyl, $-(C_1-C_6$ hydrocarbylene)(C_3-C_8 cyclohydrocarbyl), C_3-C_8 cyclohydrocarbylene)(C_3-C_8 cyclohydrocarbyl), $-(C_1-C_6$ hydrocarbylene)(C_4-C_8 heterocyclohydrocarbyl), $-(C_3-C_8$ cyclohydrocarbylene)(C_4-C_8 heterocyclohydrocarbyl), or $-O$ -aryl, or $-O-(C_1-C_6$ hydrocarbylene)-aryl; wherein said aryl, C_4-C_8 heterocyclohydrocarbyl, C_1-C_6 hydrocarbyl, C_3-C_8 cyclohydrocarbyl, C_3-C_8 cyclohydrocarbylene, and C_1-C_6 hydrocarbylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R_8 independently selected from the group consisting of C_1-C_4 hydrocarbyl, $-C_3-C_8$ 1 cyclohydrocarbyl, hydroxy, chloro, bromo, iodo, CF_3 , $-O-(C_1-C_6$ hydrocarbyl), $-O-(C_3-C_5$ cyclohydrocarbyl), $-O-CO-(C_1-C_4$ hydrocarbyl), $-O-CO-NH(C_1-C_4$ hydrocarbyl), $-O-CO-N(R_{24})(R_{25})$, $-N(R_{24})(R_{25})$, $-S(C_1-C_4$ hydrocarbyl), $-S(C_3-C_5$ cyclohydrocarbyl $-N(C_1-C_4$ hydrocarbyl) $CO(C_1-C_4$ hydrocarbyl), $-NHCO(C_1-C_4$ hydrocarbyl), $-COO(C_1-C_4$ hydrocarbyl), $-CONH(C_1-C_4$ hydrocarbyl), $-CONC_1-C_4$ hydrocarbyl)(C_1-C_2 hydrocarbyl), CN , NO_2 , $-OSO_2(C_1-C_4$ hydrocarbyl), $S^+(C_1-C_6$ hydrocarbyl)(C_1-C_2 hydrocarbyl), $-SO(C_1-C_4$ hydrocarbyl) and $-SO_2(C_1-C_4$ hydrocarbyl); and wherein the C_1-C_6 hydrocarbyl, C_1-C_6 hydrocarbylene, C_5-C_8 cyclohydrocarbyl, C_5-C_8 cyclohydrocarbylene, and C_5-C_8 heterocyclohydrocarbyl moieties of R_1 may optionally independently contain from one to three double or triple bonds; and wherein the C_1-C_4 hydrocarbyl moieties and C_1-C_6 hydrocarbyl moieties of R_8 can optionally independently be substituted with hydroxy, amino, C_1-C_4 alkyl, aryl, $-CH_2$ -aryl, C_3-C_5 cycloalkyl, or $-O-(C_1-C_4$ alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally contain one or two double or triple bonds; and wherein each heterocyclohydrocarbyl group of R_1 contains from one to three heteromoiety selected from oxygen, $S(O)_m$, nitrogen, and NR_{12} ;

R_2 is hydrogen, C_1-C_{12} hydrocarbyl, C_3-C_8 cyclohydrocarbyl, C_4-C_8

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heterocyclohydrocarbyl, -(C₁-C₆ hydrocarbylene)(C₃-C₈ cyclohydrocarbyl), -(C₃-C₈ cyclohydrocarbylene)(C₃-C₈ cyclohydrocarbyl), -(C₁-C₆ hydrocarbylene)(C₄-C₈ heterocyclohydrocarbyl), -(C₃-C₆ cyclohydrocarbylene)(C₄-C₈ heterocyclohydrocarbyl), aryl, -(C₁-C₆ hydrocarbylene)aryl, or -(C₃-C₈ cyclohydrocarbylene)(aryl); wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C₁-C₆ alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C₁-C₆ alkoxy, -OH, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, CN, and NO₂; and wherein the C₁-C₁₂ hydrocarbyl, -(C₁-C₆ hydrocarbylene), and cyclohydrocarbyl groups of 5 - 8 carbon atoms, cyclohydrocarbylene groups of 5 to 8 carbon atoms and heterocyclohydrocarbyl groups of 5 to 8 atoms of R₂ may optionally independently contain from one to three double or triple bonds; and wherein each heterocyclohydrocarbyl group of R₂ contains from one to three heteromoieties selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

or when R₁ and R₂ are as in -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₁R₂ or -NR₁R₂, R₁ and R₂ of B may form a saturated 5- to 8-membered ring which may optionally contain one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, S(O)_m, nitrogen or NR₁₂; and which carbocyclic ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, CF₃, -O-(C₁-C₄ alkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -S(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), -SO(C₁-C₄ alkyl), and -SO(C₁-C₄ alkyl), wherein one of said one to three substituents can further be selected from phenyl;

R₃ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, NH₂, NH(C₁-C₂ alkyl), N(CH₃)₂, -NHCOFC₃, -NHCH₂CF₃, S(O)_m(C₁-C₄ alkyl), CONH₂, -CONHCH₃, CON(CH₃)₂, -CF₃, or CH₂OCH₃;

R₄ is hydrogen, C₁-C₄ hydrocarbyl, C₃-C₅ cycloalkyl, -(C₁-C₄ hydrocarbylene)(C₃-C₅ cycloalkyl), -(C₃-C₅ cycloalkylene)(C₃-C₆ cycloalkyl), cyano, fluoro, chloro, bromo, iodo, -OR₂₄, C₁-C₆ alkoxy, -O- cycloalkyl), -O-(C₁-C₄ hydrocarbylene)(C₃-C₅ cycloalkyl), -O-(C₃-C₅

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cycloalkylene)(C₃-C₅ cycloalkyl), -CH₂SC(S)O(C₁-C₄ alkyl), CH₂OCF₃, CF₃, amino, nitro, -NR₂₄R₂₅, -(C₁-C₄ hydrocarbylene)-OR₂₄, -(C₁-C₄ hydrocarbylene)Cl, -(C₁-C₄ hydrocarbylene)NR₂₄R₂₅, -NHCOR₂₄, -NHCONR₂₄R₂₅, -CH=NOR₂₄, NHNR₂₄R₂₅, -S(O)_mR₂₄, -C(O)R₂₄, -OC(O)R₂₄, -C(O)CN, -C(O)NR₂₄R₂₅, -C(O)NHNR₂₄R₂₅, and -COOR₂₄, wherein the hydrocarbyl and hydrocarbylene groups of R₄ may optionally independently contain one or two double or triple bonds and may optionally independently be substituted with one or two substituents R₁₀ independently selected from hydroxy, amino, -NHCOCH₃, -NHCOCH₂Cl, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)(C₁-C₂ alkyl), -COO(C₁-C₄ alkyl), -COOH, -CO(C₁-C₄ alkyl), C₁-C₆ alkoxy, C₁-C₃ thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

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② out

R₅ is aryl or heteroaryl and is substituted with from one to four substituents R₂₇ independently selected from halo, C₁-C₁₀ hydrocarbyl, -(C₁-C₄ hydrocarbylene)(C₃-C₈ cycloalkyl), -(C₁-C₄ hydrocarbylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkyl), -(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, nitro, cyano, -NR₂₄R₂₅, -NR₂₄COR₂₅, -NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, -CON(OR₂₂)R₂₃, -CO₂R₂₆, -C=N(OR₂₂)R₂₃, and -S(O)_mR₂₃; wherein said C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, (C₁-C₄ hydrocarbylene), (C₃-C₈ cycloalkyl), (C₃-C₈ cycloalkylene), and (C₄-C₈ heterocycloalkyl) groups can be optionally substituted with from one to three substituents independently selected from C₁-C₄ alkyl, C₃-C₈ cycloalkyl, (C₁-C₄ hydrocarbylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, hydroxy, C₁-C₆ alkoxy, nitro, halo, cyano, -NR₂₄R₂₅, -NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₂)R₂₅, and -S(O)_mR₂₃; and wherein two adjacent substituents of the R₅ group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to R₅, which ring optionally can contain one, two, or three heterologous members independently selected from O, S(O)_m, and N, but not any -S-S-, -O-O-, -S-O-, or -N-S- bonds, and which ring is optionally substituted with C₁-C₄ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, nitro, halo, cyano -NR₂₄R₂₅, NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₂)R₂₅, or -S(O)_mR₂₃; wherein one of said one to four optional substituents R₂₇, can further be selected from -SO₂NH(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), SO₂NH(C₃-C₈ cycloalkyl), -SO₂NH(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -NHSO₂(C₃-C₈ cycloalkyl), -NHSO₂(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), and -NHSO₂(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl); and wherein the hydrocarbyl, and hydrocarbylene groups of R₅ may independently optionally contain one double or triple bond; R₆ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), or -(C₃

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- C_8 cycloalkylene)(C_3 - C_8 cycloalkyl), wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group; or R_6 and R_4 can together form an oxo (=O) group, or can be connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing one, two, or three heterologous ring members selected from O, SO_m , N, and NR_{12} , but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C_1 - C_4 hydrocarbyl or C_3 - C_6 cycloalkyl, wherein said C_1 - C_4 hydrocarbyl substituent may optionally contain one double or triple bond;

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② and

R_7 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C_1 - C_2)alkyl), -O(cyclopropyl), -COO(C_1 - C_2 alkyl), -COO(C_3 - C_8 cycloalkyl), -OCF₃, -CF₃, -CH₂OH or CH₂OCH₃;

R_{11} is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R_{12} is hydrogen or C_1 - C_4 alkyl;

R_{22} is independently at each occurrence selected from hydrogen, C_1 . C_{14} alkyl, C_1 . C_{14} haloalkyl, C_3 - C_6 alkenyl, C_3 . C_6 alkynyl, C_3 . C_8 cycloalkyl, (C_3 - C_8 cycloalkylene)(C_3 - C_8 cycloalkyl), and (C_1 . C_4) alkylene)(C_3 . C_8 cycloalkyl);

R_{23} is independently at each occurrence selected from C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_2 - C_8 alkoxyalkyl, C_3 - C_8 cycloalkyl, -(C_1 - C_4 alkylene)(C_3 - C_8 cycloalkyl), -(C_3 - C_8 cycloalkylene)(C_3 - C_8 cycloalkyl), aryl, -(C_1 - C_4 alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

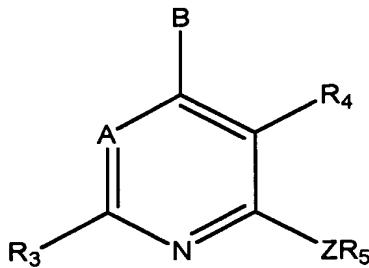
R_{24} and R_{25} are independently at each occurrence selected from hydrogen, - C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, -(C_1 - C_4 alkylene)OH, -(C_1 - C_4 alkylene)-O-(C_1 - C_4 alkyl), -(C_1 - C_4 alkylene)-O-(C_3 - C_5 cycloalkyl), C_3 - C_8 cycloalkyl, -(C_1 - C_4 alkylene)(C_3 - C_8 cycloalkyl), -(C_3 - C_8 cycloalkylene)(C_3 - C_8 cycloalkyl), - C_4 - C_8 heterocyclohydrocarbyl, -(C_1 - C_4 alkylene)(C_4 - C_8 heterocyclohydrocarbyl), -(C_3 - C_8 cycloalkylene)(C_4 - C_8 heterocyclohydrocarbyl), aryl, and -(C_1 - C_4 alkylene)(aryl), wherein the - C_4 - C_8 heterocyclohydrocarbyl groups can each independently optionally be substituted with aryl, CH₂-aryl, or C_1 - C_4 alkyl, and can optionally contain one or two double or triple bonds; or, when R_{24} and R_{25} are as $NR_{24}R_{25}$, -C(O)NR₂₄R₂₅, -(C_1 . C_4 alkylene)NR₂₄R₂₅, or -NHCONR₂₄R₂₅, then NR₂₄R₂₅ may further optionally form a 4 to 8 membered heterocyclic ring optionally containing one or two further hetero members independently selected from $S(O)_m$, oxygen, nitrogen, and NR_{12} , and optionally containing from one to three double bonds;

R_{26} is independently at each occurrence selected from C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_8 cycloalkyl, -(C_1 - C_4 alkylene)(C_3 - C_8 cycloalkyl), -(C_3 - C_8 cycloalkylene)(C_3 - C_8 cycloalkyl), aryl, and -(C_1 - C_4 alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that heterocyclohydrocarbylene groups of the compound of formula I, do not comprise any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and do not comprise more than two oxygen or S(O)_m heterologous members.

2. (Amended) A compound according to claim 1 of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is CR₇;

B is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₂OR₁₂, -CHR₂SR₁₂, -C(S)R₂ or -C(O)R₂;

Z is -NH, O, S, N(C₁-C₂ alkyl) or C(R₁₃R₁₄) wherein R₁₃ and R₁₄ are each independently, hydrogen, trifluoromethyl or methyl or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl;

R₁ is C₁-C₆ hydrocarbyl which may optionally be substituted with one or two substituents R₈ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF₃, C₁-C₄ alkoxy, -O-CO-(C₁-C₄ hydrocarbyl), -O-CO-NH(C₁-C₄ hydrocarbyl), -O-CO-N(C₁-C₄ hydrocarbyl)(C₁-C₂ hydrocarbyl), -NH(C₁-C₄ hydrocarbyl), -N(C₁-C₂ alkyl)(C₁-C₄ hydrocarbyl), -S(C₁-C₄ alkyl), -N(C₁-C₄)CO(C₁-C₄ hydrocarbyl), -NHCO(C₁-C₄ hydrocarbyl), -COO(C₁-C₄ hydrocarbyl)hydrocarbyl, -CONH(C₁-C₄ hydrocarbyl), -CON(C₁-C₄ hydrocarbyl)(C₁-C₂ alkyl), CN, NO₂, -SO(C₁-C₄ hydrocarbyl) and -SO₂(C₁-C₄ hydrocarbyl), and wherein said C₁-C₆ hydrocarbyl and the (C₁-C₄)hydrocarbyl moieties in the foregoing R₁ groups may optionally contain one carbon-carbon double or triple bond;

R₂ is C₁-C₁₂ hydrocarbyl, aryl or -(C₁-C₄ hydrocarbylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C₁-C₆ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl

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moiety of said $-(C_1-C_6 \text{ alkylene})\text{cycloalkyl}$ having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by $N-R_9$, wherein R_9 is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, $-\text{O}-\text{CO}-(C_1-C_6 \text{ alkyl})$, $-\text{O}-\text{CO}-\text{N}(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, $-\text{S}(C_1-C_6 \text{ alkyl})$, CN, NO_2 , $-\text{SO}(C_1-C_4 \text{ alkyl})$, and $-\text{SO}_2(C_1-C_4 \text{ alkyl})$, and wherein said C_1-C_{12} hydrocarbyl and the C_1-C_4 hydrocarboylene moiety of said $-(C_1-C_4 \text{ hydrocarbylene})\text{aryl}$ may optionally contain one carbon-carbon double or triple bond;

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or $-\text{NR}_1\text{R}_2$ or $-\text{CR}_1\text{R}_2\text{R}_{11}$ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3 , methylthio, methylsulfonyl, CH_2OH , or CH_2OCH_3 ;

R_4 is hydrogen, C_1-C_4 hydrocarbyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OF}_3$, CF_3 , amino, nitro, $-\text{NH}(C_1-C_4 \text{ alkyl})$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCOCH}_3$, $-\text{NHCONHCH}_3$, $-\text{SO}_n(C_1-C_4 \text{ hydrocarbyl})$ wherein n is 0, 1 or 2, cyano, hydroxy, $-\text{CO}(C_1-C_4 \text{ hydrocarbyl})$, $-\text{CHO}$, cyano or $-\text{COO}(C_1-C_4 \text{ alkyl})$ wherein said C_1-C_4 hydrocarbyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, $-\text{NHCOCH}_3$, $-\text{NH}(C_1-C_2 \text{ alkyl})$, $-\text{N}(\text{C}_1-\text{C}_2 \text{ alkyl})_2$, $-\text{COO}(C_1-C_4 \text{ alkyl})$, $-\text{CO}(C_1-C_4 \text{ alkyl})$, C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(C_1-C_6 \text{ alkyl})\text{O}(C_1-C_6 \text{ alkyl})$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{COOH}$, $-\text{COO}(C_1-C_4 \text{ alkyl})$, $-\text{CO}(C_1-C_4 \text{ alkyl})$, $-\text{SO}_2\text{NH}(C_1-C_4 \text{ alkyl})$, $-\text{SO}_2\text{N}(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{NHSO}_2(C_1-C_4 \text{ alkyl})$, $-\text{S}(C_1-C_6 \text{ alkyl})$ and $-\text{SO}_2(C_1-C_6 \text{ alkyl})$, and wherein the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

R_{12} is hydrogen or C_1-C_4 alkyl; and

or a pharmaceutically acceptable salt of such compound.

A 2
Cont

3. (Amended) A compound according to claim 2 wherein B is -NR₁R₂, -NHCHR₁R₂, -SCHR₁R₂ or -OCHR₁R₂; R₁ is C₁-C₆ hydrocarbyl, which may optionally be substituted with one hydroxy, fluoro, CF₃, or C₁-C₂ alkoxy group and may optionally contain one double or triple bond; and R₂ is benzyl or C₁-C₆ hydrocarbyl which may optionally contain one carbon-carbon double or triple bond, wherein said C₁-C₆ alkyl or the phenyl moiety of said benzyl may optionally be substituted with fluoro, CF₃, C₁-C₂ alkyl, or C₁-C₂ alkoxy.

4. (Amended) A compound according to claim 2 wherein R₁ is C₁-C₆ hydrocarbyl which may be substituted by fluoro, CF₃, hydroxy, C₁-C₂ alkyl or C₁-C₂ alkoxy and which may optionally contain one carbon-carbon double or triple bond.

A 3
B 2

13. (Amended) A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF or (b) a disorder or condition selected from inflammatory disorders, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as gastrointestinal diseases; eating disorder; hemorrhagic stress; chemical dependencies or addictions; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia; epilepsy; stroke; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition according to claim 13 for the treatment of a disorder selected from inflammatory disorders; pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception; mood disorders such as depression, and postpartum

A 3
cont

depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases; gastrointestinal diseases; eating disorders; chemical dependencies and addictions; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal, including a human.

Please cancel claims 16 - 28 without prejudice to the applicants right to file one or more divisional or continuation applications to the subject matter of these claims.

Please add new claims 29 - 40 as follows

A 4
B 3

29. A compound as claimed in claim 1 wherein R24 and R25 are selected from CF_3 , $-\text{CHF}_2$, CF_2CF_3 , and CH_2CF_3 ,
30. A pharmaceutical composition as claimed in claim 13 for treatment of a mood disorder selected from the group consisting of rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies.
31. A pharmaceutical composition as claimed in claim 13 for treatment of an inflammatory disorder selected from the group consisting of rheumatoid arthritis and osteoarthritis.
32. A pharmaceutical composition as claimed in claim 14 for treatment of depression, selected from the group consisting of major depression, single episode depression, recurrent depression, child abuse induced depression.
33. A pharmaceutical composition as claimed in claim 14 for treatment of neurodegenerative diseases selected from the group consisting of Alzheimer's disease, Parkinson's disease and Huntington's disease.
34. A pharmaceutical composition as claimed in claim 14 for treatment of chemical dependencies or addictions, selected from the group consisting of dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs.
35. A pharmaceutical composition as claimed in claim 14 for treatment of cerebral ischemia.
36. A pharmaceutical composition as claimed in claim 14 for treatment of stress